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# Craniofacial Anthropometric Pattern Profile in Hypohidrotic Ectodermal Dysplasia – Application in Detection of Gene Carriers

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## A B S T R A C T

*Hypohidrotic ectodermal dysplasia (HED) is characterized by clinical manifestations of severe hypodontia or anodontia, hypotrichosis, hypohidrosis, and specific facial appearance. Affected males show complete expression of clinical features of this condition. Their mothers, who are gene carriers, express only some signs, which are usually very mild. Currently available clinical methods are not sufficient for routine identification of the HED heterozygous gene carriers. The purpose of this study was to identify and describe the facial characteristics of HED patients and their mothers and to evaluate the usefulness of craniofacial pattern profile analysis (CFPP) in the diagnosis of this syndrome and the detection of gene carriers. In this study six affected males and their mothers were evaluated. Z-scores for each variable were calculated and compared with age- and sex-matched controls. Anthropometric analysis showed a specific dysmorphic pattern in CST patients that includes decreased skull base width (t-t: –1.67 Z); decreased forehead width (ft-ft: –1.8 Z), decreased midface depth (sn-t: – 2.02 Z), markedly decreased total facial height (n-gn: – 3.4 Z), and markedly decreased maxillary arc (t-sn-t: –2.5 Z). Gene carriers showed a similar tendency in their pattern profiles. They showed the same tendency towards lower Z-values for forehead width, facial height, and mouth width. The values for these measurements were between those of the affected and healthy controls. The most pronounced findings were increased head width (eu-eu: +2.83 Z), increased lower face width (go-go: +2.06 Z), and reduction of total facial height (n-gn: –0.95 Z). They also displayed increased nose width (al-al: +2.41 Z) and increased biocular distance (ex-ex: +2.01 Z). When used in conjunction with other methods the anthropometrics pattern profile analysis can considerably enhance detection of gene carriers for HED and increase objective assessment of the craniofacial region in HED patients.*

***Key words:*** *hypohidrotic ectodermal dysplasia, anthropometry, craniofacial pattern profile, gene carrier detection*

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## Introduction

Hypohidrotic ectodermal dysplasia (HED) is characterized by clinical manifestations of severe hypodontia or anodontia, hypotrichosis, hypohidrosis, and specific facial appearance[1–5]. The condition is usually inherited as an X-linked recessive trait, although autosomal recessive and autosomal dominant forms have been documented[3,4]. The most common form of HED, transmitted as an X-linked recessive trait, is also known as Christ -Siemens-Touraine syndrome (CSTS). Affected males show complete expression of the clinical features of this condition. Their mothers, who are gene carriers, express only some signs, which are usually very mild[2,3]. All obligate gene carriers display some dental abnormalities (hypodontia, conical crown form or slight tooth size reduction)[3,6–10]. Some gene carriers show very mild clinical expression of dental anomalies. Instead of hypodontia they manifest conically shaped crowns or mild reduction of dental dimensions. The most constant findings are conical maxillary lateral and all mandibular incisors[4–10]. Sweat pore counts are significantly decreased in all carriers to 14–16 per centimeter[1,11].

Detection of gene carriers is very important for genetic counselling. Currently available clinical methods are insufficient for routine identification of HED heterozygous gene carriers. Different procedures such as dental analysis, dermatoglyphic analysis, sweat pore counts and others have been used in the diagnosis of HED gene carriers[8,9,11]. More recently the possibility of craniofacial anthropometry has been suggested as a useful tool in carrier detection[12,13]. In the field of medical genetics clinical anthropometry is most useful in syndromology. For that purpose absolute measurements or craniofacial pattern profile analysis (CPP) is used[13–17].

The purpose of this study was to identify and describe the facial characteristics of HED patients and their mothers, and also to evaluate the usefulness of craniofacial pattern profile analysis (CPP) in the diagnosis of this syndrome and detection of gene carriers.

## Subjects and Methods

In the study six families of Croatian origin with six affected males with hypohidrotic ectodermal dysplasia (CST syndrome) and their mothers were evaluated. Physical examinations were performed in all affected males and their mothers. Standard anthropometric variables were measured in patients and female carriers as proposed by Ward[12], and Ward and Bixler[13]. Anthropometric measurements were taken according to Farkas[18]. Craniofacial pattern profile analysis (CPP) was performed in six CSTS patients and six HED gene carriers. Z-scores for each variable were calculated and compared with age- and sex-matched unrelated controls from Croatian population. Anthropometrics measurements were taken for all patients and gene carriers and Z-scores calculated for each analyzed variable (Table 1). The obtained Z-values, which fall within ±2 were considered as »normal«, whereas those falling outside these ranges were considered significantly different from controls. The deviation was regarded as mild if it amounts ±1 Z, and moderate if it ranged from 1 to 2 Z-score.

## Results

Physical examination of all the HED patients revealed characteristic facial appearance. The main observed features were sparse hair, frontal bossing, decreased lower facial height, small mouth, extroverted lips, and dry facial skin (Figures 1 and 2). In all obligate carriers

**TABLE 1**
ANTHROPOMETRIC MEASUREMENTS AND MEAN Z-SCORES IN HED PATIENTS AND HED GENE CARRIERS

| Measurements | Landmarks (Abbreviation) | Mean z-scores | |
|---|---|---|---|
| | | HED patients (N=6) | HED gene carriers (N=6) |
| 1. Head width | eu-eu | +0.53 | +2.83 |
| 2. Skull base width | t-t | –1.67 | +0.45 |
| 3. Forehead width | ft-ft | –1.80 | –0.69 |
| 4. Face width | zy-zy | –1.10 | +1.90 |
| 5. Mandible width | go-go | +0.46 | +2.06 |
| 6. Head length | g-op | –0.78 | –0.26 |
| 7. Upper third face depth | n-t | –1.22 | +0.34 |
| 8. Midle third face depth | sn-t | –2.02 | +0.63 |
| 9. Lower third face depth | gn-t | –0.90 | +1.20 |
| 10. Morphologic face height | n-gn | –3.40 | –0.95 |
| 11. Nose length | n-sn | –1.30 | –0.19 |
| 12. Nose width | al-al | –0.70 | +2.41 |
| 13. Mouth width | ch-ch | –1.42 | –0.51 |
| 14. Intercanthal distance | en-en | –1.40 | +0.83 |
| 15. Biocular distance | ex-ex | –0.40 | +2.01 |
| 16. Ear width | pra-pa | –0.88 | –0.42 |
| 17. Ear length | sa-sba | –2.00 | +1.50 |
| 18. Maxilary arc | t-sn-t | –2.50 | –0.10 |
| 19. Mandibular arc | t-gn-t | –1.70 | +0.60 |
| 20. Head circumference | head-c | –0.50 | +1.10 |

hypodontia or malformed teeth were observed (Figure 3).

Anthropometric analysis and CPP showed specific dysmorphic pattern in patients and their mothers who were gene carriers (Figure 4). CST patients manifested decreased skull base width (t-t: –1.67 Z); decreased forehead width (ft-ft: –1.8 Z), decreased midface depth (sn-t: –2.02 Z), markedly decreased total facial height (n-gn: –3.4 Z), and markedly decreased maxillary arc (t-sn-t: –2.5 Z). Gene carriers showed a similar tendency in their pattern profiles. They showed the same tendency towards lower Z-values for forehead width (ft-ft), facial height (n-gn), and mouth width (ch-ch). The values for this trait fall between those of the affected subjects and healthy controls. The same measurements were moderately to significantly decrease in HED patients. The most pronounced findings were increased head width (eu-eu: +2.83 Z) and lower face width (go-go: +2.06 Z), and reduction of total facial height (n-gn: –0.95 Z). Increased nose width (al-al: +2.41 Z) and increased biocular distance (ex-ex: +2.01 Z) were also found.

## Discussion

Application of the craniofacial anthropometrics profile (CAP) method enables comparison of genetic patients (individually or in groups) with the standard for healthy persons of the same age and sex. Correlation coefficients between the Z-values provide the means for simple com-

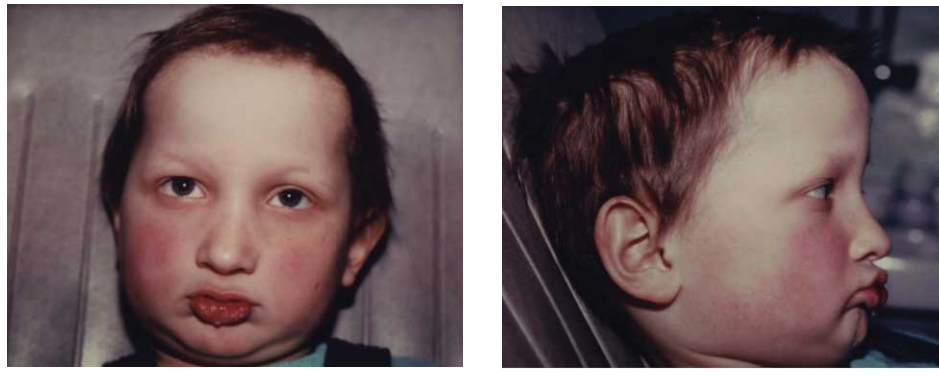

*Fig. 1. Characteristic facial appearance of patient with hypohidrotic ectodermal dysplasia (HED): A) decreased lower facial third, protruding and everted lips, and increased periorbital pigmentation. B) Lateral view of the face showing frontal bossing, sparse hair, and decreased lower facial height.*

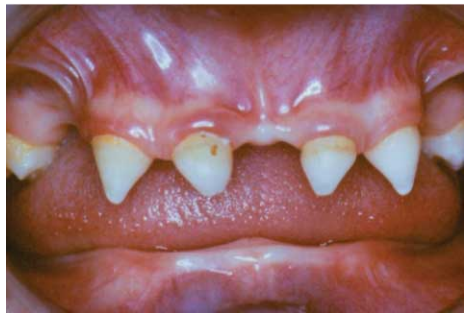

*Fig. 2. Dental findings in patient with HED: severe hypodontia and conical teeth in maxilla and anodontia in mandible.*

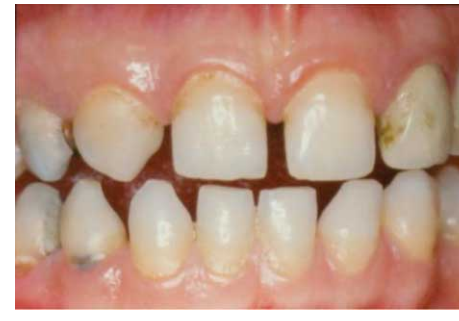

*Fig. 3. Female carrier with hypodontia of maxillary lateral incisor and smaller crown size of mandibular incisors and canines.*

parison of similarities between any two profiles. Dimensions characterised by low or high Z scores are of potential value and can serve in identification of craniofacial measurements, which deviate most from normal average values for the same age and sex. The method enables identification of the facial characteristics of affected individuals or gene carriers, which differentiate them from healthy controls. Z-values express the degree of deviations in particular facial measurements from normal control values.

Analysis of CPP enables recognition of different syndromes and precise determination of similarity or differences between syndromes in certain features of the craniofacial region[13,19]. Such a method has been successfully applied in the diagnosis of numerous syndromes, including Beckwith-Wiedemann's[20,21], Sotos syndrome[22], Down's syndrome[23–26], in identification of the heterozygous female for hypohidrotic ectodermal dysplasia[13], and many others.

Males affected with HED are characterized by clinical manifestations of hypodontia, hypotrichosis, hypohidrosis, and characteristic facial morphology. The condition is inherited as an X-linked recessive trait. The disorder shows complete

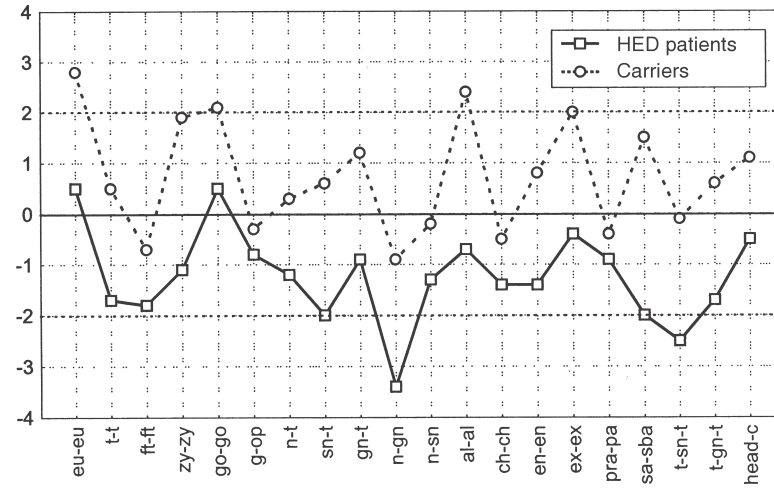


*Fig. 4. Craniofacial pattern profile analysis of patients and gene carriers.*

expression in affected males, while female carriers exhibit a wide range of signs, ranging from very mild to severe changes of affected structures. Consequently, based on a physical examination diagnosis of female carriers of the HED gene is difficult[4].

In this study anthropometric analysis of the craniofacial region in subjects with HED showed that there is significant and characteristic deviation of anthropometric measurements of the head in patients with HED and their mothers, who are obligate carriers. Affected males manifested decreased skull base width, decreased forehead width, decreased midface depth, and markedly decreased total facial height. Decreased maxillary arc was most pronounced. Similar shape of pattern profiles was observed in the gene carriers. They displayed decreased forehead width, face height, and mouth width. Anthropometric values for these measurements fall between those of the affected and healthy controls. The most pronounced findings were increased head width, increased lower face width, and reduction of total facial height. Increased nose width and increased biocular distance were also determined. Such findings enable successful use of craniofacial anthropometry in objective evaluation of the craniofacial region of individuals affected with HED as well as gene carriers of this condition.

In their study Ward & Bixler[13] showed that the faces of persons with HED were smaller in the majority of dimensions than in normal healthy persons. All values were lower than the expected Z-values, i.e. lower than zero, apart from head width and internal canthal distances. In the present study findings also showed an identical tendency. However, the pattern of reduction in craniofacial sizes was not uniform for all the subjects in this study, as found in the study of Ward & Bixler [13].

Saksena and Bixler[4] used radiographic measurements for cranial morphometric analysis of HED gene carriers. They established that gene carriers are characterised by narrow maxillary width, retrusive malar and maxillary regions, reduced lower facial height and depth,

small head height, and generalised reduction of the whole craniofacial complex.

Ward[12] showed that Z-values of the gene carrying mothers generally fall between normal values and values for HED patients. An identical tendency can be observed in this study (Figure 4). Heterozygous mothers showed reduced facial depth, reduced facial height, short nose and thin lips. Significant differences between the gene carrying mothers and healthy persons were determined for only three variables, the size of the auricle, nose width and facial width. In this study significantly reduced facial height was determined in mothers and a tendency to reduced height of the auricle. Significant increase was determined for the width of the head, lower face (go-go) and nose, compared with healthy persons.

Facial morphology of HED affected males is strikingly similar and of high diagnostic value. The use of currently available methods in clinical genetics, including mutational analysis of the EDA gene, does not allow the routine identification of the HED gene carriers. Objective delineation of facial morphology might be of help in identification of mildly affected HED gene carriers. Anthropometry can greatly enhance clinical genetic analysis by application of craniofacial pattern profiles (CPP) after converting individual measurements into Z scores[12,23–28]. Other methods, which can facilitate carrier detection, are dental examination, sweat -pore counting, and dermatoglyphic analysis[6–9,29].

## Conclusions

Analysis of CPP represents a unique method, which offers the possibility of rapid visual identification of significant deviations in the craniofacial features/ characteristics of persons with HED and gene carriers in relation to findings for healthy persons. The results of CPP analysis in gene carrying women for HED show that this simple and objective method can be successfully used in combination with other methods in the detection and diagnosis of gene carriers for HED or CSTS. We consider that this method should always be used together with a clinical examination, dermatoglyphic analysis and analysis of sweat pore counts.

CPP analysis is an objective procedure in craniofacial assessment of HED gene carriers. When used in conjunction with other methods the anthropometric pattern profile analysis can considerably enhance detection of gene carriers for HED and increase objective assessment of the craniofacial region in HED patients.

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## KRANIOFACIJALNI ANTROPOMETRIJSKI PROFIL KOD HIPOHIDROTIČNE EKTODERMALNE DISPLAZIJE – PRIMJENA U OTKRIVANJU NOSIOCA GENA

## S A Ž E T A K

Hipohidrotičnu ektodermalnu displaziju (HED) karakterizira klinička pojava jake hipodoncije ili anodoncija, hipotrihoza, hipohidroza i karakterističan izgled lica. Zahvaćeni muškarci potpuno ispoljavaju klinička obilježja toga stanja. Njihove majke, koje su nosioci gena, ispoljavaju samo neke znakove stanja koji su uglavnom vrlo blagi. Suvremeni klinički postupci nisu dostatni za rutinsku identifikaciju heterozigota nosioca gena za hipohidrotičnu ektodermalnu displaziju. Svrha ovog istraživanja je bila identificirati i opisati facijalna obilježja pacijenata s HED i njihovih majki. Cilj je bio također evaluirati korisnost izrade kraniofacijalnog antropometrijskog profila (KAP) u dijagnozi toga sindroma i prepoznavanju nosioca gena. U šest zahvaćenih obitelji hrvatske populacije (šest muškaraca i njihovih majki) provedena je kraniofacijalna antropometrija i KAP analiza. Za svaku varijablu izračunate su Z-vrijednosti i uspoređene s kontrolnim podacima zdarvih osoba iste dobi i spola. Antropometrijska analiza je pokazala specifičan dismorfični obrazac u HED pacijenata koji je uključivao smanjenu širinu baze lubanje (t-t: –1.67 Z), smanjenu širinu čela (ft-ft: –1.8 Z), smanjenu dubinu srednjeg lica (sn-t: –2.02 Z), jako smanjenu ukupnu visinu lica (n-gn: –3.4 Z) i jako smanjen maksilarni luk (t-sn-t: –2.5 Z). Nosioci gena pokazivali su sličnu tendenciju u njihovim antropometrijskim profilima. Pokazivale su tendenciju prema niskim Z vrijednostima za širinu čela, visinu lica i širinu usta. Vrijednosti tih mjera padale su između onih zahvaćenih i zdravih osoba. Najizraženiji nalazi bili su povećana širina glave (eu-eu: +2.83 Z), povećana donja širina lica (go-go: +2.06 Z) i smanjena ukupna visina lica (n-gn: –0.95 Z). Oni su također pokazivali povećanu širinu nosa (al-al: +2.41 Z) i povećanu biokularnu udaljenost (ex-ex: + 2.01 Z). Kad se primjeni zajedno s drugim metodama, KAP analiza može značajno olakšati otkrivanje nosioca gena za HED i povećati objektivnu procjenu kraniofacijalne regije u HED pacijenata.